IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2016 Vol.:6, Issue:4
© All rights are reserved by Anjani Solankee et al.

Synthesis, Characterization and *In Vitro* Antimicrobial Activity of Some New 2,3-Disubstituted-4-Thiazolidinone and 2,3-Disubstituted-5-Methyl-4-Thiazolidinone Derivatives As a Biologically Active Scaffold

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Anjani Solankee

Department of Chemistry, B. K. M. Science College, Valsad - 396001, Gujarat.

Veer Narmad South Gujarat University, Surat, Gujarat, India.

Submission: 5 July 2016
Accepted: 10 July 2016
Published: 25 July 2016

HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: 4-Amino-N-methyl acetanilide; Schiff base; 4-Thiazolidinone; Antimicrobial activity

ABSTRACT

In recent years, there has been a rising interest in researching and finding new antimicrobial agents from various sources to fight against microbial infectious pathogens. Therefore, a greater attention has been paid to synthesize new molecules. In this regarding a straightforward two-step protocol for the synthesis of 2,3-disubstituted-4-thiazolidinone **(4a-f)** and 2,3-disubstituted-5-methyl-4-thiazolidinone **(5a-f)** libraries has been developed from Schiff base **(3a-f)** by conventional method and screened for their *in vitro* antimicrobial activity against *Staphylococcus aureus* [MTCC-96], *Bacillus subtilis* [MTCC-441], *Escherichia coli* [MTCC-443] *Salmonella paratyphi-A* [MTCC-735] as bacterial pathogenic strains and *Fusarium solani* [MTCC-350] as fungal pathogenic strain. The newly synthesized compounds were characterized by IR, ^{1}H NMR and elemental analysis. Some derivatives exerted promising antimicrobial activity. Compounds **4d**, **4e**, **5c** and **5d** appeared as most proficient members of the series and may be used as the lead compound in a future study.

INTRODUCTION

The treatment of infectious diseases still remain essential and challenging problem due to a combination of factors including rising infectious diseases and the increasing number of multi-drug resistant microbial pathogens[1]. This imparts discovery of new antibiotics having improved potency and lesser toxicity is an exclusively important objective. There are various biologically active molecules with five membered rings containing two heteroatoms among which is the 4-thiazolidinone ring system is a core structure of various synthetic compounds and drugs molecules such as Darbufelon, Pioglitazone and Etozolin[2]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon has been considered as a wonder nucleus which shows almost all types of pharmacological properties. It belongs to an imperative cluster of heterocyclic compounds bearing sulfur and nitrogen in a five member ring[3]. They displaying a broad spectrum of biological activities such as, antimicrobial[4], antimycobacterial[5], anticancer[6], antiviral[7], antihistaminic[8], anticonvulsant[9] etc. The presence thiazolidone or thiazole ring at different positions in arylazo[10], sulfamoylphenylazo[11] or phenylhydrazono[12] moieties showed improved antimicrobial activity. Moreover, the combination of the 4-thiazolidinone ring with substituted pyran or fused azolopyrimidine moieties which are also known to having several biological activities[13]. Inspired by the above facts and in continuation of our ongoing research program[14] in the field of synthesis and potent antimicrobial 4-thiazolidinones, we aimed to synthesize some 4-thiazolidinones and investigate their antimicrobial potential against some selected antibacterial and antifungal pathogens. The synthesis of 4-thiazolidinones mentioned in this report can be done in simple steps with most of the compounds being produced in >50% overall yield.

MATERIALS AND METHODS

All reagents and chemicals for reaction were of analytical reagent (AR) grade. All the melting points were determined in open capillary method and are uncorrected. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and detection of the components were made by exposure to UV light or keeping the plates in iodine chamber. IR spectra of the synthesized compounds were obtained by preparing KBr pellet, using Shimadzu 8400 FTIR spectrophotometer. ^{1}H NMR studies were carried out on the Bruker Avance 400 F (MHz) spectrometer. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), br (broadened), m (multiplet). Elemental analysis was carried out by Perkin-Elmer 2400 series-II elemental analyzer

(Perkin-Elmer, USA). Reference drugs used for antimicrobial evaluation were Chloramphenicol, Streptomycin and Griseofulvin of commercial grade.

General procedure for the preparation of *N*-4-benzylidineamino-(phenyl/substituted phenyl)-N-methylacetamide (3a-f):

N-4-benzylidineamino-(phenyl/substituted phenyl)-N-methylacetamide **(3a-f)** were achieved by reacting the 4-amino-N-methyl acetanilide **(1)** (0.01mol) with appropriate aromatic aldehyde **(2a-f)** (0.01mol) in toluene using Dean-Stark water separator as the reported procedure explained previously[15].

General procedure for the preparation of 2-(phenyl/substituted phenyl)-3-(4'-N-methyl-N-acetylamino) phenyl-4-thiazolidinone (4a-f):

A mixture of Schiff base **(3a-f)** (0.01 mol) and mercaptoacetic acid (0.015 mol) dissolved in toluene were taken in 250 ml round bottom flask attached with Dean-Stark water separator and were refluxed for 12 hours. The progress of the reaction was monitored by TLC using toluene: methanol (12:8 V/V) eluent as mobile phase. After completion of the reaction, the mixtures were poured into evaporating disk and allow to evaporated excess toluene to remove. Then the fallout product was treated 5 to 6 times with saturated solution of sodium bicarbonate to remove excess mercaptoacetic acid. The product **(4a-f)** thus obtained was filtered, washed with water and recrystallized from methanol. The physical and analytical data are given in **Table1** and their spectral data are given below.

2-Phenyl-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4a):

IR (KBr, $v_{max,}$ cm^{-1}): 3024 (aromatic =CH str.), 2953 (C-H str.of alkane) 1674 (C=O str. of thiazolidinone), 1525 (aromatic C=C str.), 1390 (CH_3 str.), 1380 (C-N str.), 1223 (asymmetric C-O-C str. of ether linkage), 814 (C-H bending 1,4 disubstituted benzene ring), 678 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.4 (s, 3H, C-CH_3), 3.0 (s, 3H, N-CH_3), 4.2 (m, 2H, -CH_2, thiazolidinone ring), 5.9 (s, 1H, -CH, thiazolidinone ring), 7.0-8.0 (m, 9H, Ar-H).

2-(2'-Chlorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4b):

IR (KBr, $v_{max,}$ cm^{-1}): 3053 (aromatic =CH str.), 2908 (C-H str.of alkane) 1671 (C=O str. of thiazolidinone), 1529 (aromatic C=C str.), 1345 (CH_3 str.), 1338 (C-N str.), 1241 (asymmetric C-O-C str. of ether linkage), 720 (C-H bending 1,2 disubstituted benzene ring), 761 (C-Cl str.), 654 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.7 (s, 3H, C-CH_3), 3.2 (s, 3H, N-CH_3), 4.1 (m, 2H, -CH_2, thiazolidinone ring), 6.3 (s, 1H, -CH, thiazolidinone ring), 7.3-7.9 (m, 8H, Ar-H).

2-(3'-Bromophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4c):

IR (KBr, $v_{max,}$ cm^{-1}): 3097 (aromatic =CH str.), 2902 (C-H str.of alkane) 1690 (C=O str. of thiazolidinone), 1536 (aromatic C=C str.), 1337 (CH_3 str.), 1331 (C-N str.), 1238 (asymmetric C-O-C str. of ether linkage), 689 (C-H bending 1,3 disubstituted benzene ring), 590 (C-Br str.), 675 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.5 (s, 3H, C-CH_3), 2.9 (s, 3H, N-CH_3), 4.7 (m, 2H, -CH_2, thiazolidinone ring), 7.1 (s, 1H, -CH, thiazolidinone ring), 7.2-7.8 (m, 8H, Ar-H).

2-(3'-Phenoxyphenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4d):

IR (KBr, $v_{max,}$ cm^{-1}): 3036 (aromatic =CH str.), 2952 (C-H str.of alkane) 1659 (C=O str. of thiazolidinone), 1534 (aromatic C=C str.), 1392 (CH_3 str.), 1364 (C-N str.), 1212 (asymmetric C-O-C str. of ether linkage), 710 (C-H bending 1,3 disubstituted benzene ring), 703 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.0 (s, 3H, C-CH_3), 3.3 (s, 3H, N-CH_3), 4.5 (m, 2H, -CH_2, thiazolidinone ring), 6.1 (s, 1H, -CH, thiazolidinone ring), 6.8-8.1 (m, 13H, Ar-H).

2-(4'-Fluorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4e):

IR (KBr, $v_{max,}$ cm^{-1}): 3112 (aromatic =CH str.), 2901 (C-H str.of alkane) 1702 (C=O str. of thiazolidinone), 1582 (aromatic C=C str.), 1359 (CH_3 str.), 1323 (C-N str.), 1220 (asymmetric C-O-C str. of ether linkage), 1045 (C-F str.), 821 (C-H bending 1,4 disubstituted benzene ring), 664 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.4 (s, 3H, C-CH_3), 2.2 (s, 3H, N-CH_3), 2.9 (m, 2H, -CH_2, thiazolidinone ring), 6.4 (s, 1H, -CH, thiazolidinone ring), 6.7-7.4 (m, 8H, Ar-H).

2-(2,3'-Dichlorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-4-thiazolidinone (4f):

IR (KBr, $v_{max,}$ cm^{-1}): 3053 (aromatic =CH str.), 2937 (C-H str.of alkane) 1690 (C=O str. of thiazolidinone), 1525 (aromatic C=C str.), 1378 (CH_3 str.), 1362 (C-N str.) 1250 (asymmetric C-O-C str. of ether linkage), 753 (C-Cl str.), 729 and 813 (C-H bending 1,2 and 1,4 disubstituted benzene ring), 680 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.6 (s, 3H, C-CH_3), 3.5 (s, 3H, N-CH_3), 4.2 (m, 2H, -CH_2, thiazolidinone ring), 6.6 (s, 1H, -CH, thiazolidinone ring), 7.3-8.0 (m, 7H, Ar-H).

General procedure for the preparation of 2-(phenyl/substituted phenyl)-3-(4'-N-methyl-N-acetylamino) phenyl-5-methyl-4-thiazolidinone (5a-f):

A mixture of Schiff base **(3a-f)** (0.01 mol) and 2-mercaptopropionic acid (0.01 mol) dissolved in toluene were taken in 250 ml round bottom flask attached with Dean-Stark water separator and were refluxed for 12 hours. The progress of the reaction was monitored by TLC using toluene: methanol (12:6 V/V) eluent as mobile phase. After completion of the reaction, the mixtures were poured into evaporating disk and allow to evaporated excess toluene to remove. Then the fallout product was treated 5 to 6 times with saturated solution of sodium bicarbonate to remove excess 2-mercaptopropionic acid. The product **(5a-f)** thus obtained was filtered, washed with water and recrystallized from methanol. The physical and analytical data are given in **Table1** and their spectral data are given below.

2-Phenyl-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5a):

IR (KBr, $v_{max,}$ cm^{-1}): 3050 (aromatic =CH str.), 2920 (C-H str.of alkane) 1665 (C=O str. of thiazolidinone), 1515 (aromatic C=C str.), 1398 (CH_3 str.), 1331 (C-N str.), 1235 (asymmetric C-O-C str. of ether linkage), 810 (C-H bending 1,4 disubstituted benzene ring), 675 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.6 (d, 3H, CH-CH_3), 1.8 (s, 3H, C-CH_3), 3.2 (s, 3H, N-CH_3) 4.2 (q, 1H, -CH-CH_3, thiazolidinone ring), 6.0 (s, 1H, -CH-Ar, thiazolidinone ring), 7.2-8.0 (m, 9H, Ar-H).

2-(2'-Chlorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5b):

IR (KBr, $v_{max,}$ cm^{-1}): 3081 (aromatic =CH str.), 2954 (C-H str.of alkane) 1680 (C=O str. of thiazolidinone), 1527 (aromatic C=C str.), 1378 (CH_3 str.), 1346 (C-N str.), 1214

(asymmetric C-O-C str. of ether linkage), 752 (C-Cl str.), 731 (C-H bending 1,2 disubstituted benzene ring), 692 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.9 (d, 3H, CH-CH_3), 2.3 (s, 3H, C-CH_3), 3.6 (s, 3H, N-CH_3) 4.5 (q, 1H, -CH-CH_3, thiazolidinone ring), 5.8 (s, 1H, -CH-Ar, thiazolidinone ring), 7.0-7.8 (m, 8H, Ar-H).

2-(3'-Bromophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5c):

IR (KBr, $v_{max,}$ cm^{-1}): 3071 (aromatic =CH str.), 2942 (C-H str.of alkane) 1703 (C=O str. of thiazolidinone), 1548 (aromatic C=C str.), 1392 (CH_3 str.), 1362 (C-N str.), 1240 (asymmetric C-O-C str. of ether linkage), 681 (C-H bending 1,3 disubstituted benzene ring), 662 (C-S-C linkage), 567 (C-Br str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.2 (d, 3H, CH-CH_3), 2.4 (s, 3H, C-CH_3), 3.1 (s, 3H, N-CH_3) 4.7 (q, 1H, -CH-CH_3, thiazolidinone ring), 5.9 (s, 1H, -CH-Ar, thiazolidinone ring), 7.2-7.7 (m, 8H, Ar-H).

2-(3'-Phenoxyphenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5d):

IR (KBr, $v_{max,}$ cm^{-1}): 3212 (aromatic =CH str.), 3046 (C-H str.of alkane) 1656 (C=O str. of thiazolidinone), 1570 (aromatic C=C str.), 1374 (CH_3 str.), 1362 (C-N str.), 1247 (asymmetric C-O-C str. of ether linkage), 706 (C-H bending 1,3 disubstituted benzene ring), 603 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.8 (d, 3H, CH-CH_3), 2.5 (s, 3H, C-CH_3), 3.9 (s, 3H, N-CH_3) 4.4 (q, 1H, -CH-CH_3, thiazolidinone ring), 5.7 (s, 1H, -CH-Ar, thiazolidinone ring), 7.2-8.2 (m, 13H, Ar-H).

2-(4'-Fluorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5e):

IR (KBr, $v_{max,}$ cm^{-1}): 3123 (aromatic =CH str.), 3012 (C-H str.of alkane) 1716 (C=O str. of thiazolidinone), 1503 (aromatic C=C str.), 1356 (CH_3 str.), 1321 (C-N str.), 1243 (asymmetric C-O-C str. of ether linkage), 1089 (C-F str.), 816 (C-H bending 1,4 disubstituted benzene ring), 654 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.6 (d, 3H, CH-CH_3), 2.8 (s, 3H, C-CH_3), 3.3 (s, 3H, N-CH_3) 3.9 (q, 1H, -CH-CH_3, thiazolidinone ring), 4.7 (s, 1H, -CH-Ar, thiazolidinone ring), 7.0-7.9 (m, 8H, Ar-H).

2-(2,3'-Dichlorophenyl)-3-(4'-N-methyl-N-acetylamino)phenyl-5-methyl-4-thiazolidinone (5f):

IR (KBr, $v_{max,}$ cm^{-1}): 3102 (aromatic =CH str.), 3069 (C-H str.of alkane) 1681 (C=O str. of thiazolidinone), 1593 (aromatic C=C str.), 1370 (CH_3 str.), 1349 (C-N str.), 1210 (asymmetric C-O-C str. of ether linkage), 760 (C-Cl str.), 730 and 702 (C-H bending 1,2 and 1,3 disubstituted benzene ring), 629 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.6 (d, 3H, CH-CH_3), 2.9 (s, 3H, C-CH_3), 3.7 (s, 3H, N-CH_3) 4.0 (q, 1H, -CH-CH_3, thiazolidinone ring), 5.2 (s, 1H, -CH-Ar, thiazolidinone ring), 6.8-7.5 (m, 7H, Ar-H).

Table 1. The physical and analytical data of the synthesized compounds (4a-f) and (5a-f)

Compound	R	Molecular Formula	Yield (%)	M. P ^{0}C	Elemental analysis Calculated (Found) %		
					C	H	N
4a	Phenyl	$C_{18}H_{18}N_2O_2S$	72	Limpid	66.25 (66.15)	5.55 (5.49)	8.58 (8.50)
4b	2-Chlorophenyl	$C_{18}H_{17}N_2O_2SCl$	78	98	59.91 (59.85)	4.74 (4.78)	7.76 (7.65)
4c	3-Bromophenyl	$C_{18}H_{17}N_2O_2SBr$	70	105	53.33 (53.20)	4.22 (4.17)	6.91 (6.80)
4d	3-Phenoxyphenyl	$C_{24}H_{22}N_2O_3S$	68	Limpid	68.89 (68.80)	5.29 (5.36)	6.69 (6.60)
4e	4-Fluorophenyl	$C_{18}H_{17}N_2O_2SF$	80	167	62.79 (62.70)	4.97 (4.91)	8.13 (8.02)
4f	2,3-Dichlorophenyl	$C_{18}H_{16}N_2O_2SCl_2$	74	Limpid	54.68 (54.60)	4.08 (4.14)	7.08 (7.0)
5a	Phenyl	$C_{19}H_{20}N_2O_2S$	84	Limpid	67.05 (67.00)	5.92 (5.84)	8.23 (8.20)
5b	2-Chlorophenyl	$C_{19}H_{19}N_2O_2SCl$	79	Limpid	60.88 (60.80)	5.10 (5.16)	7.47 (7.40)
5c	3-Bromophenyl	$C_{19}H_{19}N_2O_2SBr$	67	Limpid	54.41 (54.30)	4.56 (4.61)	6.68 (6.60)
5d	3-Phenoxyphenyl	$C_{25}H_{24}N_2O_3S$	75	Limpid	69.44 (69.35)	5.59 (5.50)	6.48 (6.40)
5e	4-Fluorophenyl	$C_{19}H_{19}N_2O_2SF$	77	Limpid	63.68 (63.60)	5.34 (5.39)	7.82 (7.70)
5f	2,3-Dichlorophenyl	$C_{19}H_{19}N_2O_2SCl_2$	81	Limpid	55.74 (55.65)	4.66 (4.62)	6.83 (6.75)

Methodology for antibacterial activity

All the newly synthesized compounds were screened for their antibacterial activity by employing cup-plate agar diffusion method[16] against Gram positive and Gram negative bacteria such as *Staphylococcus aureus* [MTCC-96], *Bacillus subtilis* [MTCC-441], *Escherichia coli* [MTCC-443] and *Salmonella paratyphi-A* [MTCC-735]. The compounds were tested at 40 µg/ml concentration and DMF was used as solvent. The sterilized nutrient agar media [2.4% (w/v) agar-agar, 5% (w/v) NaCl, peptone, pH (6.8 to 7.0)] was poured into a Petri dish (9.0 cm in diameter) and allowed to set for 2 hours. On the surface of the media microbial suspension was spread over the agar plates to solidify. A stainless steel cylinder (pre-sterilized) was used to bore the cavities. All the synthesized compounds (40 µg/ml) in DMF were placed serially in the cavities with the help of micropipette. It is then allowed to diffuse for 10 minutes in refrigerator. The plates were incubated at 37 ^{0}C for 24 hours. The control was also maintained with 0.1 ml of DMF in similar manner and the zone of inhibition of the growth was measured in mm **(table 1)**. The standard known antibiotics like Chloramphenicol and Streptomycin were used.

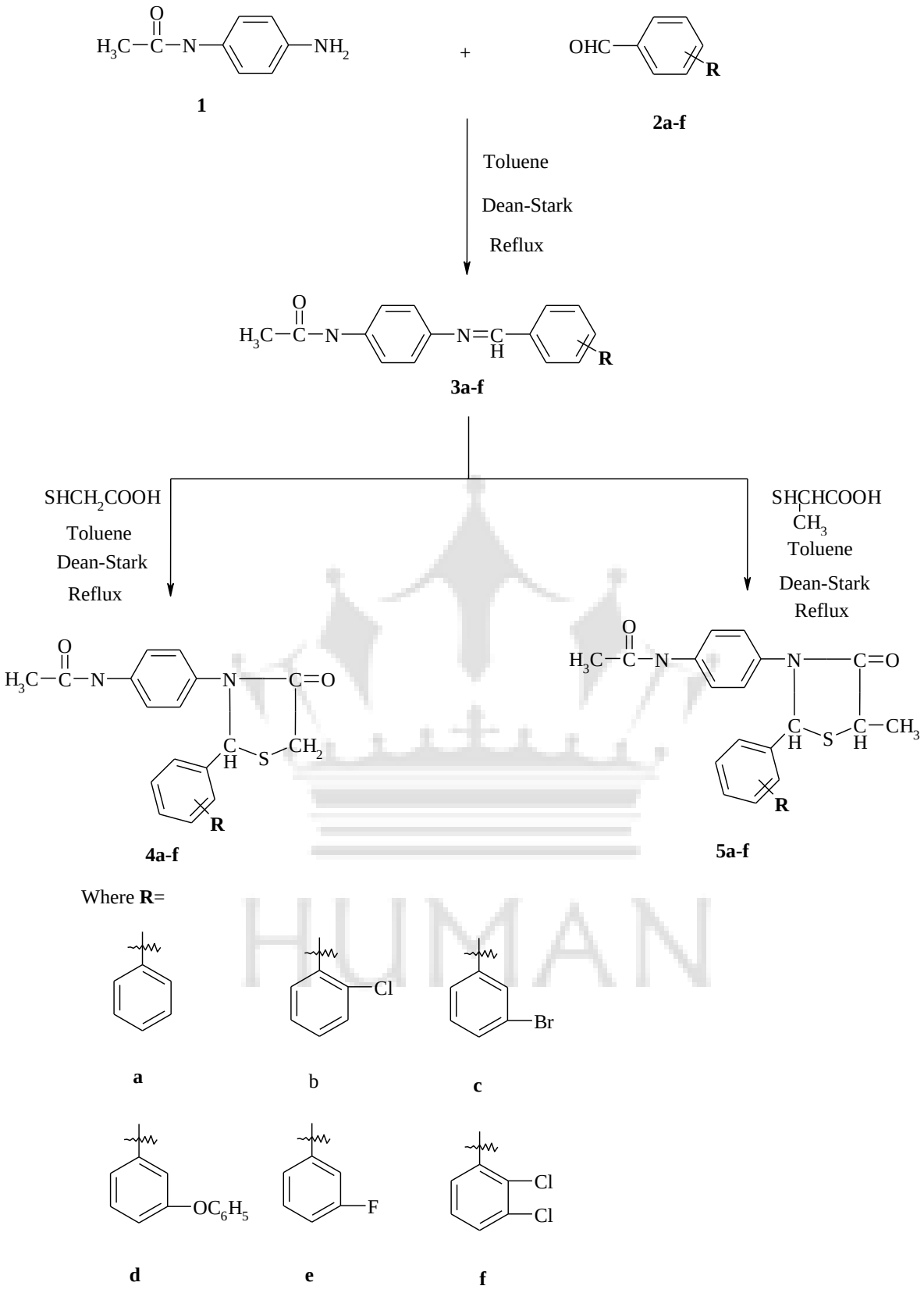
Methodology for antifungal activity

The antifungal activity of the all the synthesized compounds were carried out by applying poisoned food technique. Fungus which has been selected for inclusion in the test is *Furasium solani* [MTCC-350]. Seven days old cultures are used for collecting spores. Standard potato dextrose agar medium is used. Density of spore suspension can be determined in blood counting cell (Haemocytometer) and the final concentration is adjusted to 50,000 spores/ml. This gives about 35 spores in low power field (15× 16 mm). Spores are applied to slides by means of one to two ml pipette. Two pairs of drops are kept on each slide, four drops being in a staged position. Each drop is approximately 0.05 ml on a plain glass, such a drop would spread to a diameter of about 10 mm. For both spore production in test fungus cultures and for germination, the temperature is kept between 20-25 ^{0}C. Spores are examined 20-24 hrs. The standard known antifungal drug Griseofulvin was used.

RESULTS AND DISCUSSION

Chemistry

A two new series of 2,3-disubstituted-4-thiazolidinone and 2,3-disubstituted-5-methyl-4-thiazolidinone were achieved by cyclocondensation reaction between schiff bases and mercaptoacetic acid or 2-mercaptopropionic acid using Dean-Stark water separator as describe systematic path in reaction **scheme 1**. The structure of all the synthesized compounds was recognized from their physical, spectral and analytical data. As an example, the IR spectrum of the synthesized compound **4a** shows the strong absorption band at1674 and 678 cm^{-1} confirmed the presence of cyclic amido C=O group and C-S-C linkage of 4-thiazolidine unit. There was no absorption in the region of 1605-1621 cm^{-1} which signifying the disappearance of azomethine group in this structure. A broad stretching band for the C-N functionality and CH_3 group of 4-amino-N-methyl acetanilide ring is observed at 1380 cm^{-1} and 1390 cm^{-1} respectively. The asymmetric C-O-C stretching ether linkage, C-H bending vibrations for 1, 4 disubstituted benzene ring and =CH functionality of aromatic ring were observed at 1223, 814 and 3024 cm^{-1} respectively. The ^1H NMR spectrum of compound **4a** exerting a signal as multiplet at δ 4.2 ppm and singlet at δ 5.9 ppm due to the active methylene functionality and Ar-CH proton of the 4-thiazolidine unit. The additional remaining nine aromatic protons emerged as a multiplet signal at δ 7.0-8.0 ppm. Now the IR spectrum of compound **5a** displayed sharp strong absorption band at 1665 cm^{-1} due to the presence of cyclic amido C=O group of 4-thiazolidine ring. The C-S-C linkage and CH_3 functionality of the ring were observed at 675 and 1398 cm^{-1} respectively. There was no absorption in the region of 1605-1621 cm^{-1} which suggesting the disappearance of azomethine group in this structure and appearance of 4-thiazolidinone unit. A broad stretching band for the C-N functionality of 4-amino-N-methyl acetanilide ring is observed at 1331cm^{-1}. The asymmetric C-O-C stretching ether linkage, C-H bending vibrations for 1,4 disubstituted benzene ring and =CH functionality of aromatic ring were observed at 1235, 810 and 3050 cm^{-1} respectively. The ^1H NMR spectrum of compound **5a** signified a signal at δ 1.8, 4.2 and 6.0 ppm as a singlet, quartet and singlet due to the CH_3 proton, CH_3-CH and CH-Ar proton of the 4-thiazolidine unit respectively. The additional remaining nine aromatic protons observed as a multiplet signal at δ 7.2-8.0 ppm. Further, the obtained elemental analysis values are also in good agreement with their theoretical data.



Scheme 1. Systematic path to synthesize design compounds (4a-f) and (5a-f)

Evaluation of antimicrobial activity

The antibacterial activity of all the synthesized compounds was tested *in vitro* against pathogenic bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Salmonella paratyphi-A*. The obtained screening results were compared with standard drugs (Chloramphenicol and Streptomycin) and tabulated in **Table 2**. In case of Gram positive bacteria, compounds **5a** (8 mm), **5b**, and **5f** (9 mm), **4d**, **4f**, and **5c** (10 mm) and **5d** (13 mm) displayed a significant zone of diameter whereas compounds **4a**, **4b**, **4c**, **4e** and **5e** exerted no zone of diameter against *Staphylococcus aureus* as compared to Chloramphenicol and Streptomycin. Against *Bacillus subtilis*, compounds **4d**, **4e**, and **5d** (8 mm) and **4f** (9mm) found to possess promising activity while the remaining compounds **4a**, **4b**, **4c**, **5a**, **5b**, **5c**, **5e** and **5f** found to possess poor activity as compared to standard antibiotics Chloramphenicol and Streptomycin. In the case of Gram negative bacteria, compounds **5d** (8 mm), **5C** (9 mm), **5a** (10 mm), **4c**, and **5b** (12 mm) and **4e** (15 mm) exerted appreciable activity whereas the remaining compounds **4a**, **4b**, **4d**, **4f**, **5e** and **5f** exerted moderate activity as compared to Chloramphenicol and Streptomycin. Against *Salmonella paratyphi-A* only one compound **5f** (8 mm) showed a zone of diameter while the remaining compounds did not show zone of diameter as compared to Chloramphenicol and Streptomycin. The antifungal activity of all the synthesized compounds was tested *in vitro* against pathogenic fungal stain *Furasium solani*. Griseofulvin was used as standard antifungal drug. The scrutinize the data of antifungal activity reveals that compounds **4c**, and **5e** (52), **5c** (50) and **4e** (56) found good inhibition as compared to Griseofulvin while other compounds showed good to mild inhibition.

Table 2. *In Vitro* antimicrobial activity of synthesized compounds (4a-f) and (5a-f)

Compound	Antibacterial activity (Diameter of zone inhibition at 40 µg/ml)				Antifungal activity % Inhibition
	Gram positive		Gram negative		
	S. aureus **MTCC 96**	***B. subtilis*** **MTCC 441**	***E. coli*** **MTCC 443**	***S. paratyphi-A*** **MTCC 735**	***F. solani*** **MTCC 350**
4a	-	-	-	-	20
4b	-	-	-	-	33
4c	-	-	12	-	52
4d	10	8	-	-	33
4e	-	8	15	-	56
4f	10	9	-	-	37
5a	8	-	10	-	23
5b	9	-	12	-	42
5c	10	-	9	-	50
5d	13	8	8	-	37
5e	-	-	-	-	52
5f	9	-	-	8	37
Chloramphenicol	20	22	14	18	-
Streptomycin	25	14	28	18	-
Griseofulvin	-	-	-	-	83

CONCLUSION

In outline, we have disclosed an efficient and economic conventional method for the synthesis of 4-thiazolidinones having potentially interesting biological antimicrobial properties. From the antimicrobial screening result, it is clear that most of the prepared compounds showed improved activity against the Gram-positive bacteria rather than Gram-negative bacteria. Upon varying the substitution on aryl ring appended to the 4-thiazolidinone ring, the activities changed drastically. Among the twelve newly synthesized compounds, analogues **4d**, **4e**, **5c** and **5d** possessing electron withdrawing atom/group such as phenoxy, chloro and bromo at the meta or para position were identified as the most potent antimicrobial agents. The results described here merit further investigations in our laboratory using a forward chemical genetic approach in finding lead molecules as antimicrobial agents.

ACKNOWLEDGMENT

Author is thankful to the Principal, B. K. M. Science College, Valsad for providing necessary laboratory facilities, Atul Ltd. (Atul) for the FTIR analysis, RSIC Punjab University for the ^{1}H NMR as well as elemental analysis. We are also grateful to microbiology department, B. K. M. Science College, Valsad for antimicrobial screening facilities.

REFERENCES

1. Muroi, H., Nihei, K., Tsujimoto, K., Kubo, I. (2004). Synergistic effects of an acardiac acids and methicillin against methicillin resistant Staphylococcus aureus. Bioorganic & Medicinal Chemistry, 12 (3), 583-587.
2. Lesyk, R. B., Zimenkovsky, B. S. (2004). 4-Thiazolidones: Centenarian history, current status and perspectives for modern organic and medicinal chemistry. Current Organic Chemistry 8, (16), 1547-1577.
3. Jain, A. k., Vaidya, A., Ravichandran, V., Kashaw, S. K., Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: a review. Bioorganic & Medicinal Chemistry, 20(11), 3378-3395.
4. Solankee, A. N., & Patel R. B. (2013). Synthesis of Schiff base and 4-oxo-thiazolidinones of 5-bromo furan-2-carbohydrazide and their derivatives as an antimicrobial agents. Advances in Applied Science Research, 4 (5), 1-4.
5. Aridoss, G., Amirthaganesan, S., Kim, M. S., Kim, J. T., Jeong, Y. T. (2009). Synthesis, spectral and biological evaluation of some new thiazolidinones and thiazoles based on t-3-alkyl-r-2,c-6-diarylpiperidin-4-ones. European Journal of Medicinal Chemistry, 44 (10), 4199-4210.
6. Ottanà, R., Carotti, S., Maccari, R., Landini, I., Chiricosta, G., Caciagli, B., Vigorita, M. G., Mini, E. (2005). *In vitro* antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I. Bioorganic & Medicinal Chemistry Letters, 15 (17), 3930-3933.
7. Rawal, R. K., Prabhakar, Y. S., Katti, S. B., De Clercq, E. (2005). 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT Inhibitors. Bioorganic & Medicinal Chemistry, 13 (24), 6771-6776.
8. Previtera, T., Vigorita, M. G., Bisile, M., Orsini, F., Benetollo, F., Bombieri, G. (1994). 3,3′-Di [1,3-thiazolidine-4-one] system. VI. Structural and conformational studies on configurational isomers with antihistaminic activity. European Journal of Medicinal Chemistry, 29 (4), 317-324.
9. Siddiqui, N., Arshad, M. F., Khana, S. A., & Ahsan, W. (2010). Sulfonamide derivatives of thiazolidin-4-ones with anticonvulsant activity against two seizure models: synthesis and pharmacological evaluation. Journal of Enzyme Inhibition and Medicinal Chemistry, 25 (4), 485-491.
10. Ergenç, N., Ozçekiç, H., (1988). Synthesis and characterization of new 2-(arylidenehydrazino)-4-methyl-5-(arylazo)thiazoles. Pharmazie, 43 (12), 832-834.
11. Fadda, A. A., El-badraw, A. M., Refatb, H. M., & Abdel-Latifa, E. (2016). Synthesis of some new 2-substituted-4-sulfamoylphenylazothiophene and/or thiazole derivatives as antibacterial agents. Phosphorus, Sulfur, and Silicon and the Related Elements, 191 (5), 778-785.
12. Mahmoud, A. M., Salem, O. I. A, Abdel Moty, S. G., & Abdel Alim, A. M. (2013). Synthesis and antimicrobial evaluation of some new thiazoline and thiazolidinone derivatives incorporating [1,2,4]triazolo[1,5-a] benzimidazole. Indian Journal of Pharmaceutical Sciences, 75 (5), 545-556.
13. Svetlik, J., Veizerová, L., Mayer, T. U., Catarinella, M. (2010). Monastrol analogs: A synthesis of pyrazolopyridine, benzopyranopyrazolopyridine, and oxygen-bridged azolopyrimidine derivatives and their biological screening. Bioorganic & Medicinal Chemistry Letters, 20 (14), 4073–4076.
14. Solankee, A. N., Patel, K. P., & Patel, R. B. (2012). Efficient synthesis and pharmacological evaluation of some new 4-thiazolidinones and 5-arylidenes. Archives of Applied Science Research, 4 (1), 72-77.
15. Solankee, A. N., & Patel, R. B. (2013). Synthesis and antimicrobial activity of new Schiff base containing 4-oxothiazolidines and their spectral characterisation. Journal of Chemical and Pharmaceutical Research, 5 (7), 1-6.

16. Barry, A. L. (1976). The Antimicrobial Susceptibility Test: Principle and Practices. Illus, L. ed. Febiger, Philadelphia, Pa, USA.